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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,957	02/19/2002	Yukio Kato	KATO=21	8967

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,957	KATO ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-27* is/are pending in the application.

4a) Of the above claim(s) *7,11-15 and 17-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9 and 11-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 30 March 2005 has been received and entered in full. Claims 1-6, 8-9, and 16 have been amended, claim 10 has been cancelled, and claims 17-27 have been added.

2. Newly submitted claims 17-27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 17-27 are drawn to newly introduced methods of stimulating cartilage formation or stimulating chondrogenesis.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 7 and 11-15 remain withdrawn from further consideration as being drawn to a non-elected group. Applicants assert at page 8 of the response (filed 30 March 2005) that claims 7 and 11-15 have been amended to read upon the elected group of the polypeptide of SEQ ID NO:4. Applicant's arguments (filed 30 March 2005) have been fully considered but they are not persuasive. It is noted that claims 7 and 11-15 have not been amended and remain drawn to a non-elected invention.

5. This application contains claims drawn to an invention nonelected with traverse in Paper No. 22 April 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

6. Therefore, Claims 7, 11-15, and 17-27 are withdrawn from further consideration as discussed above, and claims 1-6, 8-9, and 16 are the subject of this Office Action. It is noted that

the pending claims have been examined to the extent that they read on the elected invention of human MTF encoded by the nucleic acid set forth in SEQ ID NO:4

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

8. The objection to the drawings as set forth at pages 3-4 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicant's amendments (filed 30 March 2005).

9. The objection to claim 1 as set forth at page 4 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

10. The objection to claims 1-3 for encompassing non-elected inventions as set forth at page 4 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

11. The objection to claims 8-10 as set forth at page 4 in the previous Office Action (mailed 30 June 2004) for failing to further limit the subject matter of a previous claim is withdrawn in view of Applicants amendments to claims 8-9 and cancellation of claim 10 (filed 30 March 2005).

12. The rejection of claims 1-6 and 16 under 35 U.S.C. §101 as set forth at page 5 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendment of said claims which now recite "isolated" (filed 30 March 2005).

13. The rejection of claims 1 under 35 U.S.C. §112(2), as set forth at pages 5-6 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendment of claims 1, 6-7, and 9, and cancellation of claims 3, 10, and 14-15 (filed 30 March 2005).

14. The rejection of claims 2-6 and 8-10 under 35 U.S.C. §112(2), as set forth at page 6 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments and cancellation of claim 10 (filed 30 March 2005).

15. The rejection of claim 2 under 35 U.S.C. §112(2), as set forth at page 6 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

16. The rejection of claims 2 and 3 under 35 U.S.C. §112(2), as set forth at page 6 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

17. The rejection of claim 8 under 35 U.S.C. §112(2), as set forth at page in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

18. The rejection of claims 1, 5, 6, 8, and 16 under 35 U.S.C. §112(2), as set forth at page 7 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendments (filed 30 March 2005).

19. The rejection of claims 8 and 9 under 35 U.S.C. §102(b) as being anticipated by Jefferies et al, as set forth at page 8 in the previous Office Action (mailed 30 June 2004) is withdrawn in view of Applicants amendment of claims 8 and 9 which now recite a specific composition (filed 30 March 2005).

Maintained Objections and/or Rejections

Claim Objections

20. Claim 2 is objected to because of the following informalities:

21. Incorrect word "transferring" at the beginning of line 6 of claim should be "transferrin".

22. Incorrect term "68 C" at line 9 of the claim should be "68° C".

23. Incorrect term "5" at line 10 of the claim should be "5 X"

24. Although not indefinite, the Examiner requests for the purpose of clarity that the phrase "an activity of membrane-bound transferrin protein for stimulating chondrogenesis activity" in claim 2 be replaced with the following: "an activity of membrane-bound transferring protein comprising stimulating chondrogenesis activity". Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, 2nd Paragraph

25. Claim 9 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons set forth at page 7 in the previous Office Action (mailed 30 June 2004).

26. Applicants argue at page 11 of the response (filed 30 March 2005) that one skilled in the art can readily ascertain what is an insulin-like growth factor. Applicants have also submitted two papers which refer to insulin-like growth factors.

27. Applicant's arguments have been fully considered but they are not persuasive for the following reasons. The itinerary of the Gordon Research Conference on "Insulin-Like Growth Factors in Physiology & Disease" submitted by the Applicants only supports the Examiner's position that there are numerous insulin-like growth factors (IGFs), including numerous insulin-like growth factor binding proteins. Furthermore, the description of insulin-like growth factor 1 (IGF-1) provided by the Applicants is not relevant since it merely describes a specific insulin-like growth factor, namely, IGF-1. Therefore, without knowing which insulin-like growth factor, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 112, 1st Paragraph (Enablement)

28. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

29. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated human membrane-bound transferrin-like protein (MTF) and insulin, does not reasonably provide enablement for a composition comprising an isolated membrane-bound transferrin-like protein (MTF) and an MTF activating agent or an insulin-like growth factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

30. The factors considered when determining if the disclosure satisfies the enablement

requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

31. Claims 8 and 9 are drawn very broadly to compositions comprising an isolated membrane-bound transferrin-like protein (MTF) and an MTF activating agent or an insulin-like growth factor. The Specification teaches that the addition of insulin or the supernatant of a chondrocyte culture results in a marked differentiation of chondrocytes in an MTF overexpressing cell line (See page 7, lines 11-11 and Figures 4-5; page 7, lines 23-26 and Figure 6). However, the Specification does not teach a commensurate number of the claimed MTF activators. The disclosure of methods of screening candidate compounds to identify potential MTF activators is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The requirement of 35 U.S.C. § 112(1) enablement is to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *make* and *use*", not *make* and *test*. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert

denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily be able to generate all the possible compounds that have the desired activity of activating MTF. Furthermore, Applicants have provided little or no guidance beyond insulin and a component of the supernatant of a chondrocyte culture to enable one of ordinary skill in the art to determine, without undue experimentation, the structure of other active compounds that may be produced or isolated and identified from the supernatant of the chondrocyte culture.

32. Due to the large quantity of experimentation necessary to generate the infinite number of MTF activating agents recited in the claims and possibly screen same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and the absence of working examples directed to same; the complex nature of the invention; and the breadth of the claims which fail to recite any structural limitations; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

33. It was found in Ex parte Maizel (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, or a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in In re Hyatt, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

34. Claim 8 is also rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

35. The Specification teaches two species of "compound" which are capable of activating the chondrogenesis stimulating activity of MTF, namely, the addition of *insulin* or the *supernatant of a chondrocyte culture* results in a marked differentiation of chondrocytes in an MTF overexpressing cell line. However, claim 8 recites an MTF activating agent. The claim does not require that the compound possess any particular structure, or other disclosed distinguishing feature. Thus, the claim is drawn to a genus of polypeptide molecules. However, the description of two "compounds" is not adequate written description of an entire genus of functionally equivalent compounds which encompasses a myriad of potentially diverse chemical compounds whose production has not been adequately described in the specification.

36. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in claim 8

is the desired activity of activating MTF. The specification does not identify any particular structure/function correlation or biological activity. The distinguishing characteristics of the claimed genus are not described. The only adequately described species are insulin and the supernatant of a chondrocyte culture. Accordingly, the specification does not provide adequate written description of the claimed genus.

37. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

38. With the exception of the "compounds" referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed agents, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

39. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

40. Therefore, only insulin and the supernatant of a chondrocyte culture, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

41. Claims 1-6 and 16 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Jefferies et al. (WO 94/01463) for reasons set forth at page 8 in the previous Office Action (mailed 30 June 2004). Jefferies et al. teach a human p97 protein (See page 2, lines 23-24) that is membrane-associated (See page 2, line 29) and transferrin-like (See page 3, lines 3-8). They teach a human p97 protein that shares 100% sequence homology with SEQ ID NO:4 of the Instant Application (See pages 102-106, SEQ ID NO:1, GenBank Accession No. AAR47899). Further, Jefferies et al. teach a soluble form of p97 (See page 9, lines 17-23) and that the soluble form of p97 lacks the GPI anchor region (See page 9, lines 11-15; Page 10, line 35 - Page 11, line 7; See also Figure 14). Lastly, Jefferies et al. teach compositions comprising the human p97 protien (See page 13, lines 12-24). Thus, Jeferies et al. meet all the limitations of claims 1-6 and 16.

42. Applicants argue at page 12 of the response (filed 30 March 2005) that Jefferies et al. does not disclose or suggest that the p97 protein can be used for stimulating chondrogenesis.

43. Applicant's arguments have been fully considered but they are not persuasive for the following reasons. The patentability of the claimed compounds rests on the particular compound, not the mechanism of action of that compound nor the inherent properties of said

compound, since a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *In re Swinehart and Sfiligoj*, 169 USPQ 226 (CCPA 1971)). Simply stating a new property of the p97 protein of Jefferies et al. does not render the composition comprising only the p97 protein of the instant application free of the art.

Summary

44. No claim is allowed.

45. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
June 3, 2005

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER